REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. CLAIM STATUS & AMENDMENTS

Claims 1-25 were pending in this application when last examined.

Claims 1-5, 9-17 and 21-24 were examined on the merits and stand rejected.

Claims 6-8, 18-20 and 25 were withdrawn as non-elected subject matter.

Claims 1 and 13 are amended to include the full name of the abbreviated amino acids at the first appearance of the abbreviation in the claims. Support can be found in original claim 1 and the disclosure, for example, at page 7, lines 13-27.

Claim 1 is amended to recite "the nucleotide sequence of SEQ ID NO: 1" instead of "a nucleotide sequence of SEQ ID NO: 1" as suggested by the Examiner at page 3 of the Office Action. Support can be found in original claim 1.

New dependent claims 26 and 27 have been added. Support can be found in the disclosure, for example, at page 3, line 15 to page 4, line 6 and in original claims 1 and 6.

No new matter has been added.

Claims 1-27 are pending upon entry of this amendment.

II. CLAIM OBJECTION

In item 5 on page 2 of the Office Actions, claims 1-5, 9-17 and 21-24 were objected for minor informalities for reciting "Tyr", "Phe", "Gln", "Asn", "Arg" and "Lys". The Office has indicated that the claims should be revised to include the full name of the abbreviated terms at their first appearance in the claims.

The present amendment overcomes this objection for the claims have been amended as suggested by the Examiner to recite the full name of the abbreviated amino acids at the first appearance in the claims.

Thus, the objection to claims 1-5, 9-17 and 21-24 is untenable and should be withdrawn.

III. WRITTEN DESCRIPTION REJECTION

In item 6 on pages 2-5 of the Office Actions, claims 1-5 and 9-12 were newly rejected under 35 U.S.C. § 112, first paragraph, on the basis that Specification lacks written description support for the claimed invention. In the second paragraph on page 3 of the Action, it is indicated that the use of "a" in "a nucleotide sequence of SEQ ID NO: 1" reads on a single amino acid found within SEQ ID NO: 1.

The present amendment overcomes this rejection objection for the claims have been amended as suggested by the Examiner at page 3 of the Office Action to recite "the nucleotide sequence of SEQ ID NO: 1".

Thus, the written description rejection of claims 1-5, 9-17 and 21-24 under 35 U.S.C. § 112, first paragraph is untenable and should be withdrawn.

IV. ENABLEMENT REJECTION

In item 7 on pages 5-8, claims 1-5, 9-17 and 21-24 were newly rejected under 35 U.S.C. § 112, first paragraph, on the basis that Specification lacks enablement for how to make and use the claimed invention. Specifically, at the top of page 6 of the Action, it was indicated that the claims read on "gene therapy" as they encompass products that are intended to be used for administration into cells. At page 6 of the Action, it was indicated that the working examples of the Specification are drawn to administration of the protein or methods of making the instantly claimed invention.

This rejection is respectfully traversed as applied to the amended and new claims.

To start, kindly note the claims are directed to genetically engineered cDNA, isolated polynucleotides, isolated cells and recombinant vectors, as opposed to gene therapy, methods of treatment or pharmaceutical compositions.

It is acknowledged that one disclosed use for the claimed polynucleotide is gene therapy. However, this is not the only disclosed use for the present invention and the protein it encodes. In addition to gene therapy, the Specification discloses other non-therapeutic *in vitro* uses. Notwithstanding that the Specification is enabled for such *in vivo* therapeutic uses, it is respectfully submitted that the Office has improperly discounted the disclosed *in vitro* uses for which the Specification is also enabled.

One utility of the claimed cDNA disclosed in the Specification is the production of the improved protein or polypeptide of claims 6-8, 18-20 and 24 (which are withdrawn from prosecution). See for instance, the working example in Example 2 on page 16, which clearly discloses routine techniques for making and using an isolated cell comprising the polynucleotide of SEQ ID NO: 1. See also Example 9 on page 24, which discloses preparation of the protein encoded by the claimed polynucleotide.

The improved protein, which is encoded by the claimed invention, can be used, for example, as an active ingredient for a drug, *i.e.*, as an apoptosis inhibitor. See pages 10-12 of the Specification. In this regard, the improved protein of Bcl-xL having the protein-transduction-domain peptide traverses the cell membrane and enters cells and inhibits apoptosis and cell death.

Moreover, the Specification at page 11 discloses that the improved protein acquiring such ability to traverse cell membranes can be utilized, for example, as follows:

(1) To maintain cells to be used for implantation in a normal state over a long period of time;

(2) To maintain organs to be used for transplantation of organs in a normal state over a long period of time;

(3) To maintain organs subjected to hemostasis in a stable state during a surgical operation;

(4) As a therapeutic for cell death caused by cerebral ischemia accompanying cerebral thrombosis, etc.;

(5) As a therapeutic for fulminant hepatitis;

(6) As a preventive for cell death caused by excess administration of steroid hormones;

(7) As a therapeutic for diseases accompanied by muscular atrophy (e.g., muscular dystrophy, myasthenia, myopathy, etc.) caused by death of myocytes; and

(8) As a preventive for the death of skin epithelial cells caused by injury or burn.

Thus, in addition to the disclosed *in vivo* therapeutic uses, the Specification clearly discloses non-therapeutic *in vitro* uses for the claimed genetically engineered cDNA, isolated polynucleotides, isolated cells and recombinant vectors.

For instance, the present invention can be used to produce the improved protein, which in turn, can then be used to maintain cells for implantation in a normal state over a long period of time. Another disclosed use is to maintain organs to be used for transplantation of organs in a normal state over a long period of time.

Moreover, it is respectfully submitted that the disclosed *in vitro* uses are enabled by the Specification.

See for instance, Example 11 on page 26, which demonstrates that introduction of TAT-Bcl-xFNK into the chondrocyte of cartilage slice culture inhibits cell death.

Also, Example 5 on pages 20-21 investigated the resistance of the transfectant FDC-P1bcl-xFNK cells prepared in Example 2 to a variety of apoptosis-inducing stimuli. The results confirmed that the transfectants expressing the improved Bcl-xFNK exhibited higher

resistance than the transfectant expressing the wild-type Bcl-xL to apoptosis induced by depletion of IL-3, and that they could grow even in the absence of IL-3. See Fig. 16.

See also Example 4 on pages 18-19, which demonstrated that transfectants expressing the improved Bcl-xFNK exhibited high resistance to all of the cytotoxic drugs tested. See Figs. 5-11.

Also, Example 12 on page 27 demonstrated that administration of TAT-Bcl-xFNK to mice the inhibited cell death of hepatocytes caused by steroid hormones.

Thus, it is clear that the Specification clearly teaches numerous *in vitro* uses for the invention. Moreover, given such disclosure and in view of the knowledge in the art, the skilled artisan would be able use the present invention, without undue experimentation, to produce the improved protein, which can then be utilized in the above-discussed *in vitro* uses. Again, kindly note the claims are directed to genetically engineered cDNA, isolated polynucleotides, isolated cells and recombinant vectors, as opposed to gene therapy, methods of treatment or pharmaceutical compositions. Also, the Office has not presented any arguments or evidence as to why these *in vitro* uses are non-enabled. For these reasons, the Specification is enabled for the claimed invention.

Lastly, Applicants direct the Examiner to Example G (Gene therapy) in the PTO's Training Materials For Examining Patent Applications With Respect To 35 U.S.C. § 112, First Paragraph - Enablement Chemical/Biotechnological Applications, which were presented to Examiners to assist them in training for enablement rejections under 35 U.S.C. § 112, first paragraph. A copy of Example G (pages G1-G6) is enclosed herewith for the Examiner's convenience. Example G relates is a gene therapy example, which involved claims to a viral vector, a pharmaceutical composition and a method of introducing a gene of interest into cells. In this example, the viral vectors and non-pharmaceutical compositions (such as the polynucleotide) were deemed to be enabled, despite the lack of enablement for the pharmaceutical/gene therapy claims. They were considered enabled on the basis that (1) the

Specification disclosed *in vitro* uses for the viral vector; and (2) the state of the art was such that using viral vectors to insert genes into cells *in vitro* is well known and is used in the field for protein production and as a research tool.

Therefore, it is clear the Office should not reject the present claims when the Specification clearly enables *in vitro* uses regardless of the disclosed *in vivo* uses. In this regard, the above-noted training Example is instructive for the instant application.

In view of the above, the enablement rejection of claims 1-5, 9-17 and 21-24 under 35 U.S.C. § 112, first paragraph, is untenable and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below

Respectfully submitted,

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ATTACHMENT

1. Example G of PTO's Training Materials For Examining Patent Applications With Respect To 35 U.S.C. § 112, First Paragraph - Enablement Chemical/Biotechnological Applications. (7 pages)

TABLE OF CONTENTS

TRAINING MATERIALS FOR EXAMINING PATENT APPLICATIONS WITH RESPECT TO 35 U.S.C. SECTION 112, FIRST PARAGRAPH -- ENABLEMENT CHEMICAL/BIOTECHNICAL APPLICATIONS

Example G: Gene Therapy

Specification: The specification discloses that viruses are commonly used as vectors to introduce genes into cells by first inserting the gene of interest into the DNA of the virus and then contacting the virus with the cells. The virus then infects the cells through cell binding receptors on the surface of the virus which bind to the cells and cause the virus to be internalized by the cells. Once internalized, the virus inserts its DNA, including the gene of interest, into the genome of the cell in such a manner that the gene of interest is expressed so as to produce its corresponding protein. Applicant has discovered that if viral vectors are first contacted with the recently discovered protein algernin, the algernin complexes with the cell binding receptors on the surface of the virus, changes the conformation thereof, and increases the infectivity of the viral vector by a factor of ten. Thus, the invention relates to a complex between a viral vector and algernin and is applicable to all situations where it is desirable to introduce genes into mammalian cells with a viral vector with a higher than normal rate of infectivity. Specifically, the specification discloses that the modified viral vector can be used *in vitro* for providing desired biological action in the cells, e.g., to produce useful proteins, and, when combined with a pharmaceutically acceptable carrier in a pharmaceutical composition, *in vivo* for medicinal purposes, such as gene therapy.

The specification lists several examples of viral vectors which are candidates for use within the claimed invention. The specification also provides the amino acid sequence of algernin as well as various methods of obtaining algernin suitable for use in the invention.

The specification includes several *in vitro* working examples with representative samples of viral vectors, genes of interest, and cells demonstrating

that when the viral vectors are complexed with algernin, the complex shows a higher rate of infectivity. The examples further demonstrate that the gene of interest in the infected cells is then expressed so as to produce its corresponding protein. The specification does not show any examples relating to gene therapy or any *in vivo* use of the viral vectors.

Claims:

1. A viral vector comprising:

a virus comprising a cell binding receptor on the surface thereof and a gene of interest, not normally present in the virus, inserted within the DNA of the virus; and

algernin complexed to the cell binding receptor of the virus.

2. A pharmaceutical composition comprising a therapeutically effective amount of the complex of claim 1 and a pharmaceutically acceptable carrier.

3. A method for introducing a gene of interest into a cell comprising contacting said cell with the viral vector of claim 1.

State of the Prior Art: The state of the prior art is such that using viral vectors to insert genes into cells *in vitro* is well known and is used in applications such as protein production and as a research tool.

Orkin et al., December 7, 1995, "Report and Recommendation of the Panel to Assess the NIH Investmen in Research on Gene Therapy", issued by the National Institutes of Health - This reference teaches that using viral vectors to insert genes into cells *in vivo* for therapeutic purposes, i.e., gene therapy, is highly

unpredictable and undeveloped in view of the complexity of *in vivo* systems.

Analysis:

The specification discloses an *in vitro* use for the viral vector of claim 1 and clearly discloses how to make and use the viral vector in the *in vitro* environment. Since claim 1 does not recite any environment of use, only one enabled use covering the scope of the claim is needed to enable the claim. Therefore, the disclosure with respect to the *in vitro* use of the viral vector is sufficient to enable claim 1 and it would be inappropriate to include claim 1 in a rejection under 35 U.S.C. 112, first paragraph.

With respect to claim 2, the "pharmaceutical composition", "therapeutically effective", and "pharmaceutically acceptable carrier" language in combination with the fact that the only disclosed pharmaceutical use of the compositions is for gene therapy leads to the conclusion that this claim should be evaluated in terms of whether the specification teaches how to make and use the composition for gene therapy. Since the specification fails to provide any guidance regarding gene therapy, such as dosages, routes of administration, and working examples, and the state of the prior art is such that gene therapy is unpredictable and undeveloped, it would be reasonable to conclude that it would require an undue amount of experimentation to determine the therapeutically effective amounts and use the compositions for gene therapy. For the reasons set forth above with respect to claim 1, it is clear that non-therapeutic compositions would be enabled. Since some compositions are enabled, it would be best to make a scope rejection of claim 2 using form paragraph 7.31.03.

Claim 3 is a broad claim. When read in light of the specification, it covers *in vitro* applications as well as *in vivo* gene therapy applications. Thus, claim 3 must be evaluated as to whether the specification enables the entire scope of the

claim. From the above discussion with respect to claims 1 and 2, it is clear that the specification enables the *in vitro* aspects of the claim but not the *in vivo* gene therapy aspects of the claim. Therefore, it would be reasonable to make a scope rejection of claim 3 using form paragraph 7.31.03.

Rejection:

Claims 2-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabled for non-therapeutic compositions and *in vitro* uses of the viral vector of the invention, does not reasonably provide enablement for pharmaceutical compositions and their use *in vivo* for gene therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 2 is directed to a pharmaceutical composition comprising a specific viral vector, the only disclosed use of the composition being *in vivo* gene therapy. Claim 3 is directed to a method which encompasses of using the specific viral vector for *in vivo* gene therapy. However, the specification fails to adequately teach how to make the composition having a "therapeutically effective amount" of the viral vector and how to use the composition and vector for *in vivo* gene therapy. Gene therapy is a highly unpredictable and undeveloped field and the skill in the art is high. See Orkin et al. which states:

> 2. While the expectations and the promise of gene therapy are great, clinical efficacy has not be definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful

therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols.

3. Significant problems remain in all basic aspects of gene therapy.

The specification fails to disclose the intended patients, amounts of the viral vector to be administered, what amount is considered to be therapeutically effective, the route and time course of administration, the sites of administration, the intended therapeutic product, the intended disease, and the intended target organs. The specification also lacks any working examples showing that the viral vector as claimed would deliver the genes encoding the therapeutic products to the appropriate site and that the genes once delivered would be expressed sufficiently to provide adequate product to effect the desired therapy. In view of the quantity of experimentation necessary to determine the above parameters, the lack of direction or guidance presented, the absence of working examples for *in vivo* gene therapy, the breadth of the claims, and the unpredictable and undeveloped state of the art with respect to gene therapy, it would require undue experimentation for one skilled in the art to practice the entire scope of the claimed invention.

If claims 2 and 3 were limited as follows, this rejection would be overcome:

2. A composition comprising the viral vector of claim 1 and a carrier.

3. A method for introducing a gene of interest into a cell *in vitro* comprising contacting said cell with the viral vector of claim 1.